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B03

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SHIONOGI & CO LTD

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235/12, A61K 31/4184, 31/427, 31/437, 31/4439, 31/4725, 31/501,
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A61P 31/12, 31/18, 43/00, C07D 213/50

New nitrogenous heteroaromatic compounds are HIV integrase inhibitors for treating HIV infections, AIDS and AIDS related diseases (Jpn)

C2002-207360 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ
CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES
FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG
KR KZ LC LK LR LS LT LU LV MA MD MG MK MN
MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG
SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU
ZA ZM ZW) R(AT BE CH CY DE DK EA ES FI FR
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Addnl. Data: FUJI M

2002.02.27 2002WO-JP01779

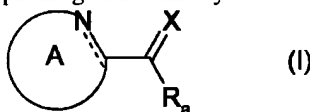
B(7-H, 14-A2B1, 14-D3, 14-G1B) .4

NOVELTY

Nitrogenous heteroaromatic compounds (I) are new.

DETAILED DESCRIPTION

Nitrogenous heteroaromatic compounds of formula (I) and their prodrugs salts and hydrates are new.



A = nitrogenous heteroaromatic;

X = O, S or NH;

R_a = C(=Z₄)R_b or nitrogenous heteroaryl attached via an atom adjacent to N;at least one of A and R_a = substituted by Z₁Z₂Z₃R₁ and both are optionally substituted by 1-6 Q;Z₄ = O, S or NH;R_b = H or Q;

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Z₁, Z₃ = bond or optionally substituted alkylene or alkenylene;
Z₂ = bond, CHO, S, SO, SO₂, SO₂NR₂, NR₂SO₂, O, NR₂, NR₂CO,
CONR₂, COO, OCO, CO or optionally substituted alkylene or
alkenylene;

Q = halo, COOAlk, COOH, OAlk, AlkOAlk, NO₂, OH, alkynyl,
SO₂Alk, SAlk, AlkSAlk, haloalkyl, haloalkoxy, cycloalkyl,
cycloalkenyl, oxo, thioxo, alkylenedioxy, alkylene, alkenylene,
nitroso, N₃, amidino, guanidino, CN, NC, SH, SO₂NH₂, NH₂SO₂,
CHO, COAlk, OCOAlk, hydrazino, morpholino or optionally
substituted Alk, alkenyl, amino, CONH₂, Ar, heterocyclyl,
AlkAr, OAr, SAr, OAlkAr, AlkOAr, AlkSAr, SO₂Ar or
SO₂AlkAr;

Alk = alkyl;

Ar = aryl or heteroaryl.

ACTIVITY

Anti-HIV.

In assays a compound of formula (I-1) had an IC₅₀ value for HIV
integrase of 0.230 micro g/ml.

MECHANISM OF ACTION

HIV-Integrase-Inhibitor

USE

As HIV integrase inhibitors for treating and preventing HIV infections, AIDS and AIDS related diseases.

ADMINISTRATION

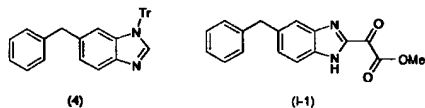
Dosage is 0.05-3000 (preferably 0.1-1000) mg/day orally or 0.01-
1000 (preferably 0.05-500) mg/day parenterally. (I) may be
administered with reverse transcriptase inhibitors and/or protease
inhibitors.

EXAMPLE

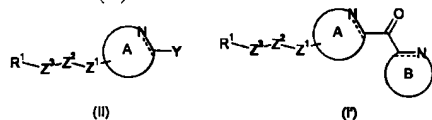
1.5 M n-Butyl lithium in hexane (4.33 ml) was added at -65°C to
a compound of formula (4) (2.25 g) in tetrahydrofuran (70 ml) and the
mixture was stirred at -65°C for 1 hour then at -40°C for 30 minutes.
Methyloxalyl chloride (0.920 ml) was added at -65°C and the mixture
was stirred at -30°C for 30 minutes. Work-up including silica gel
chromatography hexane:ethyl acetate (= 2:1) gave 628 mg (23%) of
product which was deprotected using trifluoroacetic acid to give a
compound of formula (I-1) in 82% yield.

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**TECHNOLOGY FOCUS**

Organic Chemistry - Preparation: (I) are prepared e.g. by acylating a
heteroaromatic compound of formula (II) to give a compound of
formula (I').



Y = H, Cl, Br or I.

(83pp2533DwgNo.0/0)

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